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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/796,164	02/06/97	STAMLER J	DUK96-03PA3

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EXAMINER	
CELSA, B	
ART UNIT	**PAPER NUMBER**
1654	20

DATE MAILED: 03/30/99

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

file copy

Office Action Summary

Application No.	Applicant(s)
08/796,164	Stamler et al.
Examiner	**Group Art Unit**
Bennett Celsa	1654

☒ Responsive to communication(s) filed on *Jan 6, 1999*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *10-22, 24-32, 40-46, and 63-68* is/are pending in the application.

Of the above, claim(s) *42, 45, 46, and 63-68* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *10-22, 24-32, 40, 41, 43, and 44* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

Applicant's amendment dated 1/22/99 in paper no. 18 and accompanying terminal disclaimer in paper no. 19 is hereby acknowledged. The terminal disclaimers have been entered.

Information Disclosure Statement

Applicant's fourth Supplemental Information Disclosure Statement filed 1/6/99 in paper no. 16 referring to application Serial No. 08/559,172 is acknowledged. It is noted that the Examiner has reviewed this application.

Status Of The Claims

Claims 10-22, 24-32, 40-46 and 63-68 are currently pending.

Claims 10-22, 24-32, 40-41 and 43-44 are under consideration.

Newly amended claims 42, 45 and 46; and newly added claims 63-68 are withdrawn from further consideration as being drawn to a non-elected invention.

Supplemental Restriction

Newly submitted claims 63-68 and amended claims 42, 45 and 46 are directed to inventions that are independent or distinct from the invention originally claimed for the following reasons: the amended claims address methods which differ from the original claims with respect to method objective and/or reaction conditions as to constitute patentably distinct inventions that require additional burdensome manual/computer bibliographic searches. Similarly, the newly added claims address methods which differ in method objectives and/or experimental reaction

conditions (e.g. pH, buffer etc.) and reactants as to constitute patentably distinct methods requiring different and burdensome manual/computer searches.,

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. This modified restriction, in response to applicant's amendment is hereby made FINAL.

Allowable Subject Matter

Claims 43 and 44 are allowable over the prior art of record.

Withdrawn Objection(s)/Rejection(s)

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

- The enablement rejection of claims 40-41 under 35 U.S.C. 112, first paragraph in items 2 and 3 of the prior office action is hereby withdrawn in response to applicant's amendment.

- Applicant's amendment and arguments have overcome the indefinite rejection of claims with respect to items A-E in items 4. and 5. of the prior office action. Applicant's amendment to claims 42 and 45 as to methods which are withdrawn from consideration renders consideration of the indefinite rejection of these claims moot. With respect to item "A." directed to the indefiniteness of the terms "low molecular weight thiol" and "low molecular weight nitrosothiol" the Examiner notes that applicant described techniques for evaluating molecular weight (e.g.

dialysis) and size (e.g. via selective precipitation) of proteins. Additionally, the specification on page 8, lines 21-32 provides a means for comparison of "low molecular weight nitrosothiols" (thiol amino acids) with high molecular weight thiols such as thioproteins (e.g. S-nitrosohemoglobin). Accordingly, the above combined with applicant's discussion rendered the relative term "low" definite.

- The provisional obviousness double patenting rejection of claims 17-32 and 40-41 over the 08/616,371 application and the provisional obviousness double patenting rejection of claims 10-15 over the 08/667,003 copending applications in items 9. and 10. of the previous office action are hereby withdrawn in view of applicant's submitted terminal disclaimers over the two copending applications.

- The anticipation rejection under 35 USC 102(b) (in item 13. of the prior office action) over the Moore et al. reference is hereby withdrawn since claims 42 and 45, as amended, are no longer under Examiner consideration; rendering the rejection moot.

- The obviousness rejection of claims 42, 45 and 46 (in item 14. of the prior office action) over the Moore et al. and Kharitonov et al. references is hereby withdrawn since claims 42, 45 and 46, as amended, are no longer under Examiner consideration; rendering this rejection moot.

Outstanding Rejection(s)

2. Claims 10-16 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 9-15 of copending Application No. 08/616,371. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Discussion

Applicant's arguments directed to the statutory double patenting rejection above were considered but deemed nonpersuasive for the following reason(s). Applicant asserts that claims 10-16 in the present application will be canceled upon indication of the allowance of claims 9-15 of the copending application. Accordingly, the above rejection is hereby retained.

3. Claims 10-22, 25-28, 30-32 and 40-41 under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93).

Stamler et al. discloses the therapeutic use of "low molecular weight" thiols, S-nitroso-protein and amino acid compounds (e.g. S-nitroso-hemoglobin or myoglobin) for regulating protein function, inhibiting platelet function, cellular metabolism including effecting vasodilation; increasing blood oxygen transport by hemoglobin and myoglobin; NO delivery; *in vitro* nitrosylation of molecules present in the body (e.g. see Abstract; pages 1-3 and claims). Thus, the disclosed compounds are deemed useful in treating cardiovascular disorders, brain disorders and respiratory disorders within the scope of the presently claimed invention. Stamler discloses a thionitrosylated hemoglobin composition (e.g. see page 58 and claims 13-16) comprising reacting hemoglobin in the presence of oxygen with a nitrosating agent (e.g. SNOAc). Stamler teaches the use of equimolar amounts of nitrosating agent and Hb. Optimizing nitrosylating amounts to achieve "excess" nitrosation of hemoglobin to insure nitrosylation of hemoglobin would be obvious to the skilled artisan at the time of applicant's invention. The reference method of forming thionitrosylated oxygenated hemoglobin would render obvious the formation of thionitrosylate deoxygenated hemoglobin under anaerobic conditions as presently claimed. The reference specifically discloses the use of nitrosylated proteins (e.g. S-nitroso hemoglobin) and low molecular weight nitrosating agents (e.g. see pages 1-2; page 24, lines 10-16) preparations thereof for the treatment of disorders by increasing oxygen capacity and transport; modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (E.g. see pages 19-25 and claims). The combination of nitrosating agents (e.g. thionitrosylated "Low" molecular weight and "high" molecular weight compounds; e.g. nitrosothiol, glutathione and hemoglobin) would be prima facie obvious to the skilled artisan

at the time of applicant's invention in order obtain the increased pharmaceutical effects of the agents.

4. Claims 10-22, 24-32 and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler et al. in view of Feola et al., U. S. Pat. No. 5,439,882 (8/95: filed 5/93 or earlier) and Klatz et al., U.S. Pat. No. 5,395,314 (3/95: file 6/93 or earlier).

The discussion of the teaching of the Stamler et al. reference in the above rejection under 35 USC103 is hereby incorporated by reference in its entirety. To summarize, the Stamler et al .reference discloses the use of S-nitrosating agents (e.g. low molecular weight e.g. glutathione and hemoglobin derivatives) to treat disorders by achieving a variety of physiological effects including vasodilation; radical scavenging ; NO and oxygen delivery. The above Stamler reference does not explicitly disclose the use of nitrosating agent(s) to act as a blood substitute or treat sickle cell anemia. Feola et al. disclose the use of "blood substitutes" to restore blood volume, transport oxygen and reduce vasoconstriction (e.g. vasodilate) by the use of hemoglobin alone or combined with glutathione as a blood substitute to treat blood disorders (e.g. sickle cell anemia) (e.g. see Abstract, examples and columns 1 and 7). Klatz et al. disclose a brain resuscitation and organ preservation composition which comprises perfluorocarbons which act as "a blood substitute" which "transport(s) oxygen in a manner similar to hemoglobin" (e.g. see Abstract, col. 1, col. 4, lines 1-25). The Stamler et al. reference provides the skilled artisan with motivation to use nitrosating agents alone or combined to treat disorders of diseases to which vasodilation and oxygen/NO transport would prove to be therapeutic. It would have been obvious to the skilled artisan at the time of applicant's invention to utilize thionitrosating agents (e.g. hemoglobin, glutathione) as blood substitutes to treat blood disorders such as sickle cell anemia since the Feola reference discloses the use of hemoglobin and thiol containing blood substitutes to treat anoxic blood disorders (e.g. sickle cell anemia as disclosed by Feola) and Stamler provides a reasonable expectation that nitrosating agents will be successful to achieve the desired effects of blood substitutes. It would have been obvious to the skilled artisan at the time of applicant's invention to utilize nitrosating agents for organ preservation since the Katz reference provides motivation to utilize compositions such as perfluorocarbons for their ability to act as "blood substitutes" and hemoglobin oxygen transporters and Stamler teaches that nitrosating agents would be successful to achieve the desired effects of blood substitutes and also act as effective hemoglobin oxygen transporters.

Discussion

Applicant's arguments and submitted 132 Declaration by Dr. Stamler were considered but deemed nonpersuasive with regard to the above obviousness rejections in items 3. and 4. above. The Examiner will address the Declaration evidence (and arguments) which parallel applicant's representative. The first issue raised is the missing reagent issue. The declarant points out that Example 19 fails to indicate the identity of the nitrating agent which is reacted in equimolar concentrations with hemoglobin (e.g. 12.5 uM at pH 6.9). However, it is clear that the nitrating agent is SNOAc as recited in the rejection after reading page 58, lines 17-25 and this point is easily confirmed by applicant's own previous application e.g. in Example 1 of 08/559,172, the reaction of SNOAc and hemoglobin in equimolar amounts (and presumably under the same conditions), **achieves the same spectrophotometric evidence** of S-nitrosothiol bond formation. E.g. compare Figures 28 and 29 of WO 93/09806 to Figures 1 and 2 of the 08/559,172. Accordingly, the WO 93/09806 reference undisputably discloses the reaction of a low molecular weight nitrosothiol (e.g. SNOAC) with hemoglobin. Whether applicant actually peformed the experiment or the acidified nitrate experiment in his laboratory is irrelevant to the disclosure by the reference of the reaction between SNOAc and hemoglobin. The Declarant's catching of a mistake with regard to maximum absorbance (e.g. 450nm) when the graph clearly shows a maximum absorbance of 540nm is acknowledged by the Examiner. However, the declarant's point that one can not measure or distinguish SNO-hemoglobin from hemoglobin at a particular

absorbance or that there is not any real confirmation of the presence of SNO-hemoglobin **is not the same as proving the absence of SNO-hemoglobin**. Applicant' s own specification demonstrates that reacting a low molecular weight S-nitrosothiol such as SNOAc in equimolar amounts with hemoglobin (e.g deoxy or oxy) would be expected to generate SNO-hemoglobin (e.g. see present specification at pages 46-48 and Figures 1a-1d). It is also noted that use of extrinsic evidence by the Examiner to demonstrate inherency is permitted (e.g. see MPEP 2131.01(d)), *including the use of applicant's own specification* (e.g. examples). See *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). The Declarant's attempt to reproduce the Reference Example 19 method was not found persuasive since it is unclear as to whether applicant is showing the absence of SNO-hemoglobin or the inability of the utilized assay to detect the presence of SNO-hemoglobin. It is also noted that applicant's claimed composition "comprises" SNO-hemoglobin and therefore encompasses mixtures of SNO-hemoglobin with other hemoglobin species. The Examiner also is unable to reconcile the Declarants' experimental results with those experimental results and statements in the specification which assert that reacting low molecular weight nitrosothiols with oxygenated hemoglobin in 1:1 ratio would form some amount of SNO-hemoglobin (again see specification pages 46-48 and Fig. 1a-1d); and additionally Example 1 and Figures 1 and 2 in application Serial No. 08/559,172 which confirms the presence of a "composition which comprises SNO-hemoglobin" within the scope of the presently claimed invention. The Declarant's problem regarding pH and concentration is not seen by the Examiner as problematic where one would be motivated to increase the amounts of nitrosating agent as

pointed out in the rejection and optimize other reaction parameters (e.g. pH) as a matter of course. The Declarant's further statement regarding the veracity of reference statements regarding "reaction at the heme" are again not commensurate in scope to the claims which broadly include "compositions comprising S-nitrosohemoglobins" and additionally fail to address the optimization of reaction parameters (e.g. increasing nitrating agent relative to hemoglobin) concentration which is obvious to one of ordinary skill. The Declarant's assertion that pH 6.9 cannot be used to form SNO-hemoglobin is rebutted by page 16 of 08/559,172 which appears to show the formation of S-nitrosyl hemoglobin at this pH in addition to higher pH optimums. In light of the reference disclosure, applicant's own disclosure in the present application and the disclosure provided in 08/559,172 applicant's proffered declaration and attorney argument can not be considered persuasive. It is also noted that the Declarant's and attorneys arguments are not commensurate in scope to the claimed invention; nor do they adequately address the optimization of reaction conditions specifically pointed out in the obviousness rejections above.

With regard to the second obviousness rejection above (e.g. Stamler in view of Feola and Klatz) applicant's arguments directed to the Stamler reference have already been addressed above. Applicant's argument of the Feola and Klatz references separately, is not persuasive insofar that the above rejection is clearly a combination of Stamler taken in view of Feola and Klatz. Applicant further argues that Stamler does not specifically describe any nitrosated hemoglobin or any effects of nitrosated hemoglobin. However, as pointed out in the rejection, the Stamler reference clearly *discloses* the use of nitrosylated proteins generically and nitrosylated

hemoglobin specifically to produce the desired effects. Applicant's argument regarding the inability of the Stamler reference to enable the making of specifically S-nitrosylated hemoglobin has already been addressed above. The Examiner again asserts that applicant's claims are not restricted only to the use of an S-nitrosylated hemoglobin compound but are generically broader to include a mixture of S-nitrosylated hemoglobin and other hemoglobin derivatives to which the Stamler reference is enabled by its disclosure and its examples taken separately or in view of obvious modifications thereof (e.g. optimization of reactions and experimental conditions). Accordingly, this rejection is hereby maintained.

5. Claims 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler, U.S. Pat. No. 5,583,101 (12/96: filed 7/94).

Stamler discloses a method of inhibiting or relaxing skeletal muscle contraction and disease states resulting therefrom by administering nitric oxide containing compounds (e.g. see Abstract and Patent claims) which serves to "deliver" NO or its biological equivalents to tissues (e.g. see patent column 1).. Stamler clearly includes the use of nitrosylated heme containing proteins including hemoglobin and serum albumin (e.g. see col. 2, lines 7-25: see also patent claims especially patent claims 12 and 13). Accordingly, the patent teaching of administration of a nitrosylated heme containing protein to achieve tissue delivery would have been obvious to the skilled artisan in view of the Stamler reference since the skilled artisan would have been motivated to select a nitrosylated heme protein for use in the Stamler method.

Discussion

Applicant's arguments directed to the above obviousness rejection over the '101 patent were considered but deemed nonpersuasive for the following reasons. Initially it is noted that the above rejection has been rewritten in view of applicant's amended claims. Applicant argues that the '101 patent is nonenabling for making S-nitrosylated proteins since it recites WO93/09806 which has been argued by applicant and Dr Stamler (e.g. 132 Declaration) to be nonenabling. Initially it is noted that this argument is clearly not commensurate with the scope of claim 40 which encompasses any nitrosyl heme containing donor of NO which is clearly taught by the reference patent (e.g. see patent col. 2, lines 20-21) which generically teaches the use of S-nitrosylated heme proteins which meets the claim 40 limitations. It is further noted that claim 41 is drawn to the use of **any "nitrosyl hemoglobin**" and not to S-nitrosohemoglobin. There is no evidence of record that the WO 93/09806 is nonenabled for the formation of **a nitrosyl hemoglobin**. More specifically, the teaching of the WO reference of reacting a low molecular nitrosothiol compound with hemoglobin would be expected to make an nitrosyl hemoglobin within the scope of the present claim 41. Applicant's and Dr. Stamler's argument that the 93/09806 reference fails to teach *specifically S-nitrosylated hemoglobins* is not commensurate to claim 41 which includes hemoglobin's which are not specifically S-nitrosylated. In any event, as discussed in the obviousness rejections above regarding the WO 93/09806 reference it is believed that some degree of S-nitrosylation of thiol hemoglobin groups is enabled by the WO 93/09806 reference. Accordingly, the above obviousness rejection is hereby retained.

NEW REJECTIONS

6. Claims 10, 13, 32, 40 and 41 rejected under 35 U.S.C. 102(b) as being anticipated by Stamler, WO 93/09806 (5/93) in view of Serial No. 08/559,172 in order to demonstrate inherency. E.g. See MPEP 2131.01(d).

Stamler et al. discloses the therapeutic use of "low molecular weight" thiols, including S-nitroso-hemoglobin or myoglobin NO delivery (e.g. see Abstract; pages 1-3 and claim 35. More specifically, Stamler discloses a thionitrosylated hemoglobin composition (e.g. see page 58 and claims 13-16) comprising reacting hemoglobin in the presence of oxygen with a nitrosating agent (e.g. SNOAc). In example 19, pages 58-59, Stamler teaches the use of equimolar amounts of nitrosating agent and Hb in which the nitrosating agent appears to be SNOAC. Indeed the disclosure of the use of SNOAC with hemoglobin to form S-nitrosyltated hemoglobin is confirmed by the disclosure in Example 1 of 08/559,172 which achieves the same spectrophotometric evidence of S-nitrosothiol bond formation. E.g. compare Figures 28 and 29 of WO 93/09806 to Figures 1 and 2 of the 08/559,172. Accordingly, the Stamler reference discloses the formation of a composition of a composition comprising S-nitrosohemoglobin which is oxygenated since the reaction is not conducted under oxygen removed conditions. (e.g. oxygenated) and which anticipates claims 10 and 13 of the present application. The method of present claims 32, 40 and 41 drawn to "prevention of thrombus formation" and "delivering NO" would "inherently" be anticipated by the adminstration of. S-nitrosohemoglobin in amounts and to a host within the scope of the presently claimed invention for the purposes of NO delivery (e.g.

reference claim 35) or for any other therapeutic purpose disclosed by the reference. The prior art procedure inherently must prevent thrombus formation or deliver NO because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993).

Claim Rejections - 35 USC § 101

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

A. Claims 10, 13, 32, 40 and 41 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by claims 1-3 and 6-11 of copending Application No.08/559,172 which has a common inventor with the instant application.

The '172 claims disclose S-nitrosylated human hemoglobin which would anticipate S-nitrosylated oxygenated hemoglobin presently claimed since the '172 generic would encompass

only two possible species (e.g. dexoygenated/oxygenated human hemoglobin), either of which would be immediately envisaged by one of ordinary skill in the art at the time of applicant's invention. E.g *See In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978).

Claim 11 of '172 discloses a method of treatment (e.g. ischemic injury/shock) which "administers" an S-nitrosohemoglobin compound. The method of present claim 32 drawn to prevention of thrombus formation would "inherently" be anticipated by claim 11 of '172 which administers a compound within the scope of present claim 32 (e.g. S-nitrosohemoglobin) in amounts and to a host within the scope of the presently claimed invention. The prior art procedure inherently must prevent thrombus formation because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Claim 11 also meets all the process limitations of present claims 40 and 41 since claim 11 administers (e.g. delivers) a nitrosyl heme containing compound (e.g. a nitrosylhemoglobin to a host within the scope of the presently claimed invention.

Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future patenting of the copending application. 08/559,172

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application

was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

B. Claims 10, 13, 32, 40 and 41 are rejected under 35 U.S.C. 102(f,g) as being anticipated by 1-3 and 6-11 of copending Application No.08/559,172.

The '172 claims disclose S-nitrosylated human hemoglobin which would anticipate S-nitrosylated oxygenated hemoglobin presently claimed since the '172 generic would encompass only two possible species (e.g. dexoygenated/oxygenated human hemoglobin), either of which would be immediately envisaged by one of ordinary skill in the art at the time of applicant's invention. E.g *See In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978).

Claim 11 of '172 discloses a method of treatment (e.g. ischemic injury/shock) which "administers" an S-nitrosohemoglobin compound. The method of present claim 32 drawn to prevention of thrombus formation would "inherently" be anticipated by claim 11 of '172 which administers a compound within the scope of present claim 32 (e.g. S-nitrosohemoglobin) in amounts and to a host within the scope of the presently claimed invention. The prior art procedure inherently must prevent thrombus formation because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Claim 11 also meets all the process limitations of present claims

40 and 41 since claim 11 administers (e.g. delivers) a nitrosyl heme containing comound (e.g. a nitrosylhemoglobin to a host within the scope of the presently claimed invention.

Claim Rejections - 35 USC § 103

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

a. Claims 10-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 08/559,172.

Although the conflicting claims are not identical, they are not patentably distinct from each other because '172 discloses S-nitrosylated human hemoglobin compounds and compositions thereof formed by S-nitrosylation by "low molecular weight nitrosothiols" within the scope of the presently claimed invention. The '172 claims disclose S-nitrosylated human hemoglobin which would encompass S-nitrosylated oxygenated hemoglobin presently claimed since the '172 generic would encompass only two possible species (e.g. dexoygenated/oxygenated human hemoglobin), to which it would have been obvious for one of ordinary skill to select either the deoxygenated/oxygenated hemoglobin compound

To the extent the '172 disclosure differ from the presently claimed methods by failing to utilize "excess nitrosating agent" and/or forming oxygenated hemoglobin "in the presence of oxygen" and deoxygenated hemoglobin "in the absence of oxygen" such differences would have been obvious to one of ordinary skill in the art at the time of applicant's invention. A skilled artisan wishing to optimize nitrosylation of hemoglobin would immediately consider increasing the nitrating agent relative to the concentration of the hemoglobin reactant. The patent application teaching of "human hemoglobin" would encompass both deoxygenated and oxygenated forms of hemoglobin which would routinely be nitrosylated in the presence of oxygen to retain the oxygenated hemoglobin derivative and under deoxgenated conditions to retain the deoxygenated hemoglobin. .

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

b. Claims 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over claims 1-11 of copending Application No. 08/559,172 for the same reasons as recited above regarding obviousness provisional double patenting..

7. Applicant's submission of an information disclosure statement under 37 CFR 1.97© with the fee set forth in 37 CFR 1.17(p) on 1/6/99 in paper no. 16 and Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (703)308-0254.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa

March 25, 1999